Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Recommendations on hepatitis C screening for adults.

Bibliographic Source(s)

Canadian Task Force on Preventive Health Care. Recommendations on hepatitis C screening for adults. CMAJ. 2017 Apr 24;189(16):E594-E604. [100 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
	Patient and Public Perspectives

	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▮	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▮	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▮	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▮▮▮	External Review
▮▮▮▮▯	Updating

Recommendations

Major Recommendations

The grades of recommendations (strong, weak) and grades of evidence (high, moderate, low, very low) are defined at the end of the "Major Recommendations" field.

Summary of Recommendations for Clinicians and Policy-Makers

The Canadian Task Force on Preventive Health Care (CTFPHC) recommends against screening for hepatitis C virus (HCV) in adults who are not at elevated risk (strong recommendation, very low-quality evidence).

This recommendation applies only to adults who are not at elevated risk for HCV. It does not apply to pregnant women or adults who are at elevated risk for hepatitis C, such as:

Individuals with current or history of injection drug use
Individuals who have been incarcerated
Individuals who were born, travelled or resided in HCV-endemic countries (see Appendix 6 of the original guideline document [see the "Availability of Companion Documents" field])
Individuals who have received health care where there is a lack of universal precautions
Recipients of blood transfusions, blood products or organ transplant before 1992 in Canada
Patients on hemodialysis
Individuals who have had needle-stick injuries
Individuals who have engaged in other risks sometimes associated with HCV exposure, such as high-risk sexual behaviours, homelessness, intranasal and inhalation drug use, tattooing, body piercing or sharing sharp instruments or personal hygiene materials with someone who is HCV positive
Anyone with clinical clues suspicious for HCV infection (and above risk factors)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Grades of Evidence

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — The CTFPHC is very uncertain about the estimate.

Grading of Recommendations

Strong recommendations are those for which the CTFPHC is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most people will be best served by the recommended course of action and that the recommendation can be adopted in practice or as policy in most situations. Strong recommendations are normally based on high-quality evidence (i.e., high confidence in the estimate of the effect of an intervention). Strong recommendations may recommend in favour of an intervention (when there is high confidence of benefit) or against an intervention (when there is high confidence of harm). However, there are five circumstances in which the CTFPHC may consider a strong recommendation based on low- or very low-quality evidence:

- When low-quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high)
- When low-quality evidence suggests benefit and high-quality evidence suggests harm or a very high cost
- When low-quality evidence suggests equivalence of two alternatives, but high-quality evidence of less harm for one of the competing alternatives
- When high-quality evidence suggests equivalence of two alternatives and low-quality evidence suggests harm in one alternative
- When high-quality evidence suggests modest benefits and low-/very low-quality evidence suggests possibility of catastrophic harm

Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention), but appreciable uncertainty exists. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, or there is more variability in the values and preferences of patients. In cases where the balance of cost and benefits is ambiguous, key stakeholders differ about the acceptability or feasibility of implementation, and the effects on health equity are unclear are likely to result in a weak recommendation. A weak recommendation implies that most people would want the recommended course of action, but that many would not. For clinicians, this means that they must recognize that different choices will be appropriate for each individual, and that they must help each person arrive at a management decision consistent with his/her values and preferences. Policy-making will require substantial debate and involvement of various stakeholders.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Hepatitis C

Guideline Category

Prevention

Screening

Clinical Specialty

Family Practice

Infectious Diseases

Internal Medicine

Preventive Medicine

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Physician Assistants

Physicians

Public Health Departments

Guideline Objective(s)

To provide clinicians and policy-makers with guidance on screening asymptomatic Canadian adults for hepatitis C virus (HCV)

Target Population

Asymptomatic Canadian adults who are not at elevated risk for hepatitis C

Interventions and Practices Considered

Screening for hepatitis C virus (not recommended for adults not at elevated risk)

Major Outcomes Considered

Screening for Hepatitis C Virus: a Systematic Review

- Mortality due to hepatitis C virus (HCV) infection
- Morbidity including cirrhosis (compensated or decompensated) due to HCV infection
- Hepatocellular carcinoma
- Liver transplantation

Quality of life
HCV transmission
Virologic response
Behavioural changes to improve health outcomes
Histological changes
Overdiagnosis
Overtreatment
False positives and false negatives
Harms of follow-up tests (including biopsy)
Abuse or violence
Anxiety
Cost-effectiveness
Willingness to be screened and factors considered in willingness to be screened

Treatment for Hepatitis C Virus: a Systematic Review and Meta-Analysis

Mortality (all-cause or hepatic)
Cirrhosis (compensated or decompensated)
Hepatocellular carcinoma
Hepatic decompensation
Need for liver transplantation
Quality of life
Sustained virologic response
Improvement in liver histology
Reduced HCV transmission
Withdrawals due to adverse events, neutropenia, anemia, psychological adverse events, flu-like symptoms and rash

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The recommendations were informed by two independently conducted systematic reviews that addressed specific aspects of the guideline's analytic framework. The first review was conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) and focused on screening for hepatitis C virus (HCV) infection. The second review was conducted by the Public Health Agency of Canada (PHAC) and focused on the effectiveness of newer HCV treatments compared with older treatments (see the "Availability of Companion Documents" field).

Screening for Hepatitis C Virus: a Systematic Review

Research Questions

Question 1. What is the clinical effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?

Question 2. What is the frequency of harms associated with screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?
Question 3. What is the cost-effectiveness of screening for HCV infection in asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values in Canada?
Question 4. What are the patients' preferences and values regarding HCV infection screening of asymptomatic, non-pregnant, treatment-naive adults with unknown liver enzyme values?
Question 5a: What is the clinical validity of anti-HCV antibody testing for general population screening to detect adults with chronic hepatitis C?
- Alone
- In combination with secondary antibody (Ab) or antigen (Ag) tests

Question 5b: What is the clinical validity of HCV antigen testing for general population screening to detect adults with chronic hepatitis C?
- Alone
- In dual antibody-antigen tests

Literature Search Strategy

The literature search was performed by an information specialist using a peer-reviewed search strategy according to the PRESS checklist. The search strategy described here applies to all research questions.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; EMBASE (1974–) via Ovid; the Cochrane Library via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. To address research question 1, three separate searches were performed. A broad search for the concept of screening for hepatitis C was performed, and methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, randomised controlled trials (RCTs) and controlled clinical trials. To address the specific concepts of risk and prevalence-based screening programs, no methodological filters were applied to the search to limit retrieval by study type. To address research question 2, methodological filters were applied to limit retrieval to safety data. To address research question 3, methodological filters were applied to limit retrieval to economic studies. To address research question 4, methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, randomised controlled trials and non-randomised studies. For research questions 1, 2, 3, and 4, retrieval was limited to the human population, English- and French-language documents with publication dates beginning January 2000. To address research question 5, methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, RCTs, and non-randomised studies. For research question 5, retrieval was limited to the human population, English- and French-language documents, and results were not limited by publication date. Conference abstracts were excluded from the search results. Bi-weekly database alerts were established to update the searches until February 19, 2017. See Appendix 1 of the screening systematic review for the detailed search strategy.

Grey literature (literature that is not commercially published) was identified by searching the Grey Matters checklist. Grey literature search updates were performed in March, April, May, and September 2016, which includes Web sites of regulatory agencies, health technology assessment agencies, clinical guideline repositories, and professional associations. The searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate content experts and industry.

Selection Criteria and Method

Studies suitable for inclusion were selected from those identified through the literature search using the criteria listed in Table 1 and Table 2 in the screening systematic review.

Selection Method

Four reviewers, in sets of two, independently screened titles and abstracts from the literature search and selected articles that warranted further evaluation. Full texts of potentially relevant articles identified

through the initial screen were retrieved and independently assessed by two reviewers for possible inclusion based on the predetermined selection criteria outlined in Table 1 and Table 2 of the screening systematic review. The reviewers made use of the screening checklist found in Appendix 2 of the review and compared their lists of included and excluded studies. Disagreements were resolved through discussion or third-party consultation.

Inclusion Criteria

The inclusion criteria were unique to each question. The inclusion criteria for the research questions on the clinical effectiveness of screening (Q1), frequency of screening harms (Q2), cost-effectiveness of screening (Q3), and people's preferences and values related to screening (Q4) are presented in Table 1 of the screening systematic review. The inclusion criteria for the research question on the clinical validity of general population screening with antibody and antigen tests (Q5) are presented in Table 2 of the review. With respect to study populations, studies that reported enrolling mixed categories of participants were included if they separately reported results for participants that met the inclusion criteria, or if at least 80% of the study population met the inclusion criteria. Studies that enrolled participants from the general population (including blood donors) without providing details on age, pregnancy status, symptoms, or treatment history were assumed to meet the population inclusion criteria.

As recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, prior to the start of the review, outcomes of interest to be assessed in this review for the research questions on clinical effectiveness (Q1) and harms of screening (Q2) were selected and ranked for clinical importance by members of the Canadian Task Force on Preventive Health Care's (CTFPHC's) HCV working group and by a sample of 19 adults (including people with and without HCV infection) who represented a cross-section of the general population; the number of adults with confirmed HCV infection was not reported. The input from the general population sample was gathered by an independent research group with expertise in knowledge translation at St. Michael's Hospital, Toronto, Ontario. All outcomes for Q1 and Q2 were ranked as critical (scores 7 to 9) or important (scores 4 to 6) by at least one of the groups.

For the purposes of this review, the "willingness to be screened" outcome for Q4 is reported as the number or proportion of people who did or would hypothetically accept screening for HCV, when offered. This outcome does not necessarily represent the number or proportion of participants who actually underwent screening in the context of the study or otherwise. It also does not include reporting of the reasoning behind the acceptance or rejection of the offer of screening, as this is captured by the "factors considered in the decision to be screened for HCV" outcome.

Exclusion Criteria

Duplicate publications, companion reports, narrative reviews, case series, case reports, conference abstracts, and editorials were excluded from the responses to all questions. Studies that enrolled mixed categories of participants were excluded if less than 80% of the study population met the inclusion criteria and results were not reported separately for patients who met the inclusion criteria.

For people's preferences related to HCV screening (Q4), studies that reported rates of screening uptake alone, without collecting data from participants directly regarding an offer of HCV screening during the conduct of the study, were excluded from the analysis.

For the question on the clinical validity of general population screening with antibody and antigen tests (Q5), studies were excluded if patient selection was based on known HCV status, increased risk of HCV, or on the basis of a clinical condition that may be associated with chronic HCV infection or that may impact a patient's result on an antibody or antigen test (e.g., patients with hematological malignancies, autoimmune disorders, etc.). Birth-cohort studies that limited inclusion to individuals born from 1945 to 1965 were excluded. While this group represents a subset of the general population, this birth cohort is known to be a high HCV prevalence group for whom screening is recommended in relevant guidelines produced by the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Preventive Services Task Force (USPSTF). Studies conducted in "high prevalence countries" (defined as seroprevalence greater

than 3.5% based on the CDC classification of HCV prevalence levels) according to the seroprevalence value reported for each country were excluded, as the outcomes for this question are affected by population prevalence. Evidence for these outcomes from high HCV prevalence countries is therefore unlikely to be applicable in a Canadian context, where the adult anti-HCV seroprevalence is approximately 1.1%. Studies were also excluded for Q5 if the evaluated interventions were first- or second-generation enzyme immunoassays (EIAs). For included studies in which multiple generations of EIAs were assessed, only data pertaining to third- or fourth-generation EIAs were extracted. Studies were excluded if a subset of positive samples or a subset of negative samples from the antibody or antigen testing stage, and not the entire set of samples or patients at enrollment, progressed to the polymerase chain reaction (PCR) testing stage.

Treatment for Hepatitis C Virus: a Systematic Review and Meta-Analysis

Population, Intervention, Comparator, Outcomes (PICO), Outcome Ranking, Data Sources and Searches

This review is intended to provide indirect evidence on the value of population based screening. In an effort to more closely mimic treatment in an unscreened population, the reviewers included studies where over 80% of the participants were treatment-naïve and whose participants did not have human immunodeficiency virus (HIV) co-infection, a history of liver transplantation, hemodialysis, or occupational exposure (see Table 1, Figure 1 of the systematic review).

The intervention was any currently available treatment approved for use in Canada and any emerging treatment regimens anticipated to become available in Canada by February 2016 (see Table 2 of the systematic review). The reviewers included all genotypes and our comparator was pegylated interferon alpha administered by injection plus oral ribavirin (PR) taken for 48 weeks.

The CTFPHC's HCV work group and a focus group of patients identified and rated outcomes. The focus group was conducted by an independent research group, the Knowledge Translation Program based at St. Michael's Hospital, Toronto, Ontario. Patients included former or current intravenous drug users, individuals born between 1950 and 1970, individuals from countries with high HCV prevalence and individuals who were diagnosed with HCV. All included outcomes were ranked by patients as being either critical or important.

The patient important outcomes (outcomes) included the following benefits: surrogate outcomes of reduced HCV transmission, sustained virological response and improvement in liver histology; and long term outcomes of reduced mortality (hepatic & all cause), hepatocellular carcinoma, hepatic decompensation, need for liver transplantation and improved quality of life. The harms comprised: withdrawal due to adverse events, psychological adverse events, neutropenia, flu-like symptoms, anemia and rash.

The reviewers updated the search strategy from a therapeutic review conducted by the Canadian Agency for Drugs in Technologies and Health (CADTH) in February 2015. The AMSTAR (A Measurement Tool to Assess Systematic Review) tool was used to critically appraise the methodological quality of the CADTH review (see Appendix A of the systematic review). Included drugs were approved for use in Canada or had high likelihood of approval by February 2016 (see Table 2 of the systematic review). In addition to searching the databases identified by the CADTH they also searched PubMed and ClinicalTrials.gov to November 18, 2015 and included all of CADTH's references (included and excluded studies) for study selection. The full search strategies are provided in Appendix B of the treatment systematic review. An updated search was conducted on November 18, 2016 by the Ottawa Evidence Review Synthesis Centre (see Appendix C of the systematic review).

Study Selection

Two reviewers independently screened abstracts and full texts of potentially relevant articles, extracted data from included studies and verified the accuracy and completeness of the other's data extraction. Conflicts were resolved by third party consultation. Included studies can be found in Appendix D and excluded studies can be found in Appendix E of the systematic review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart can be found in Figure 2 of the review.

Number of Source Documents

Screening for Hepatitis C Virus: a Systematic Review

A total of 12,786 records were identified through the initial database searches; 676 of these articles were selected for full-text evaluation. Of these, 40 were selected for inclusion in the review, including one article identified through subsequent alerts. Appendix 4 of the systematic review presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow charts. Lists of excluded studies, with reasons for exclusion, are provided in Appendix 5 of the review (see the "Availability of Companion Documents" field).

Treatment for Hepatitis C Virus: a Systematic Review and Meta-Analysis

A total of 490 full-text articles were screened and 11 reports were included in the review. See the PRISMA flow chart in Figure 2 of the review (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group Grades of Evidence

High quality — Further research is very unlikely to change confidence in the estimate of effect.
Moderate quality — Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low quality — Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very low quality — The Canadian Task Force on Preventive Health Care (CTFPHC) is very uncertain about the estimate.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The recommendations were informed by two independently conducted systematic reviews that addressed specific aspects of the guideline's analytic framework. The first review was conducted by the Canadian Agency for Drugs and Technologies in Health (CADTH) and focused on screening for hepatitis C virus (HCV) infection. The second review was conducted by the Public Health Agency of Canada (PHAC) and focused on the effectiveness of newer HCV treatments compared with older treatments (see the "Availability of Companion Documents" field).

Screening for Hepatitis C Virus: a Systematic Review

Data Extraction

Data were extracted from each study on the inclusion list that were relevant to the outcomes predefined

in the protocol, and entered into standardized tables as found in Appendix 3 of the systematic review. Data from figures were not used if the data points were not explicitly labelled. For all studies, descriptive data were also extracted, including information on authors, design of the study, year of publication, country, care setting, participant characteristics, description of the intervention, description of comparators (if appropriate), conflicts of interest, and financial sponsorship. Additionally, for Q3, descriptive data included perspective of the analysis, sources of utilities, main assumptions, and planned sensitivity analyses. The reviewers did not have reason to contact authors to request missing information, clarify issues, or verify extracted data.

No eligible studies were identified for Q1, and therefore no relevant outcome data were extracted. For Q2 and Q3, two reviewers independently extracted descriptive and outcome data from each included study.

For Q4, two reviewers independently inductively coded and captured statements from the results section from each included article that were relevant to the research question for subsequent analysis using NVivo qualitative data analysis software (QSR International Pty Ltd., Version 11, 2015). For further details, refer to the "Data Analysis Methods" below. Prior to coding, each result statement was assessed to ensure it was differentiated from raw data, methods, external data, and researchers' conclusions and implications; result statements meeting these criteria were coded. Variables statistically associated with the uptake of screening (e.g., age, sex) were not extracted from included studies because these data are not directly related to participant willingness to be screened, and are therefore outside the scope of this review.

For Q5, one reviewer extracted descriptive and outcome data and the other verified the accuracy of data extraction.

The reviewers met frequently throughout the process to discuss discrepancies. Disagreements were resolved through discussion or third-party consultation.

Quality Assessment and Risk of Bias Assessment

Following data extraction, an assessment of the quality of each selected study was made using an appropriate assessment tool specific to the study design. For Q2 and Q3, two reviewers independently assessed study quality. For Q4 and Q5, one reviewer assessed the quality of each study and a second reviewer verified the assessments. A Cochrane Risk of Bias Assessment Tool for Non-randomised Studies of Interventions guided comments on the quality of the study that was deemed eligible to answer Q2, and the Drummond checklist was applied to the cost-effectiveness study (Q3). For Q4, qualitative studies were assessed using criteria outlined in the Critical Appraisal Skills Programme checklist, and survey studies were assessed using standardized criteria including clarity and appropriateness of study methods, with particular attention paid to sampling decisions, validity, and reliability of data collection methods, and the comprehensiveness of reporting. The QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool was applied to critically appraise the studies on the clinical validity of general population screening with antibody (Ab) and antigen (Ag) tests (Q5).

During deliberations, the reviewers documented information used to support the quality judgments. Reviewers resolved disagreements in appraisals through discussion or third-party consultation if consensus could not be reached.

Data Analysis Methods

Frequency of Harms, Cost-effectiveness, and Clinical Validity of Screening with Ab and Ag Tests

While a meta-analysis of outcome data was planned, it was not appropriate given one study each met the criteria for the questions on frequency of harms and cost-effectiveness. No studies were identified for the question on clinical effectiveness. For the question on the clinical validity of screening tests, meta-analysis was likewise planned but not conducted given the observed clinical heterogeneity across included studies. For each research question, a narrative synthesis was conducted that involved presenting the results from each included study alongside important study and patient characteristics believed to contribute to the observed heterogeneity in narrative and table formats.

Patient Preferences and Values

For the question on the preferences and values related to the decision to be screened for HCV, a thematic analysis was conducted. The analysis was conducted in two stages: coding and development of descriptive themes. The analysis was conducted using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2015).

In the first coding stage, two reviewers independently reviewed the results reported within the full-text articles, and assigned codes to concepts, ideas, and categories relevant to the research question. Initial codes were applied in the context of the outcomes (from the Population, Intervention, Comparator, Outcome [PICO]) including people's willingness to be screened; factors considered in decisions to be screened; barriers and facilitators to screening; and preferences, values, and attitudes about screening. More codes were developed iteratively, as new concepts emerged as the analysis progressed.

To begin coding, the first three study reports were coded independently by the two reviewers. A team meeting was then held during which coding was compared and discussed, with discrepancies resolved and corresponding refinements made to the coding template. The next three reports were then coded independently, with another team meeting to allow for comparison, discussion, and refinements to the coding template. Given the high level of agreement between the researchers in terms of coding at this point, the remainder of the articles were coded by one reviewer and verified by the second reviewer. Regular discussions among the research team enabled organization, code refinement, and reflection upon a wide range of interpretations across the body of research identified. When all codes were applied to the full sample of results, all of the text assigned to each code was read independently by two reviewers to assess consistency in interpretation and application, and to determine whether any additional levels of coding were required. Refinements were made, as required, to the coded text and definitions were developed for each code to reflect the data captured within.

In the second stage of the analysis, the codes developed in the prior stage were organized into related areas to construct "descriptive themes." In this process, four reviewers met to assess similarities and differences between the codes, and grouped together all similar codes into unique themes. At this stage, reviewers determined whether emergent themes were transferable across different studies, and whether some apply to some populations but not others. Once descriptive themes were identified, a draft summary of the results across the studies organized by each theme was written by one reviewer and subsequently reviewed by a second reviewer. The final version was agreed upon by three descriptive review team members and reviewed by a fourth. It represents a synthesis that closely reflects the original results of the included studies, with minimal interpretation.

Assessment of the Overall Quality of the Evidence Using GRADE and CERQual

No study met the inclusion criteria for Q1; therefore, a GRADE assessment could not be made. A GRADE assessment was planned to assess confidence in the findings for Q2 but ultimately not conducted. According to the GRADE handbook, "the [GRADE] system is designed for reviews and guidelines that examine alternative management strategies or interventions, which may include no intervention or current best management as well as multiple comparisons." The evidence on frequency of harms (Q2) came from a single non-comparative study of the harms observed in a group of patients who went through one-time screening for HCV. As the study did not provide an estimate of effect of HCV screening relative to a comparator, the reviewers did not apply GRADE. GRADE was likewise not used to assess confidence in findings for Q3, as the methods for the assessment of evidence derived from cost-effectiveness analysis studies have not yet been established. According to the section 6.3.4.6 Economic Model of the GRADE handbook, the GRADE working group does not recommend incorporating cost-effectiveness models into evidence profiles given that economic models include a number of assumptions and evidence from multiple sources of varying quality.

The Confidence in the Evidence from Reviews of Qualitative Research (CERQual) approach (contained in the GRADE methodology tool box) guided the evaluation of the body of descriptive studies identified for Q4 of this review. The tool was used to develop a level of confidence in the review findings, based on an evaluation of the four CERQual components that include the methodological limitations, relevance,

adequacy of data, and coherence of the evidence contributing to the findings. Findings were assessed independently by one of two reviewers. Review authors were aware of the interactions between the four components of CERQual and gave equal weight to each component, while recognizing overlap between them. The reviewers began with an assessment of methodological limitations and then assessed the other three components in an iterative fashion. Each review finding began with a high level of confidence, which was reduced according to the severity of concerns about the evidence in any of the four CERQual domains.

Four reviewers met to discuss the initial CERQual assessment of the findings and come to consensus on the level of confidence. The reviewers discussed the judgments and developed a clear description of the rationale behind each assessment. Participation by multiple reviewers from different disciplinary backgrounds, including reviewers with experience in primary qualitative research and qualitative evidence synthesis, helped shape the interpretations of confidence.

Two reviewers used GRADE criteria to evaluate the evidence for Q5. These criteria were based on study design, risk of bias, indirectness, inconsistency, imprecision, and publication bias. When there was a serious or very serious concern with a criterion, the evidence was downgraded accordingly by one or two levels. Disagreements between reviewers were resolved through discussion or third-party consultation until consensus was reached.

Treatment for Hepatitis C Virus: a Systematic Review and Meta-Analysis

Data Extraction and Quality Assessment

Two reviewers independently screened abstracts and full texts of potentially relevant articles, extracted data from included studies and verified the accuracy and completeness of the other's data extraction. Conflicts were resolved by third party consultation.

The search identified randomised and non-randomised, controlled and uncontrolled interventional studies (including cost-effectiveness modelling studies [modelling]). However, to select the studies that were used to examine the impact of treatment on each outcome, following the GRADE approach reviewers used a staged approach starting from study types providing the highest quality evidence. For instance, they first searched for evidence on each individual outcome from randomised controlled trials (RCTs) and if they found evidence from RCTs, then they did not search for evidence from any other study type. If evidence on a particular outcome could not be found from RCT data, then they searched for evidence from the following study types in sequential order: non-randomised controlled, non-randomised uncontrolled, then modelling studies.

Quality assessment involved two steps. First the reviewers critically appraised the methodological quality of all studies. RCTs were appraised using the Cochrane Risk of Bias tool and modelling studies were evaluated using a CTFPHC modified Drummond checklist and the CHEERS tool (see Appendix A of the systematic review). Upon consensus of the work group, the reviewers included the modelling study with highest methodological quality, and which reported on the greatest number of patient important outcomes by fibrosis score compared to the others (see Appendix A of the review). Next, they assessed the strength and quality of the body of evidence for each patient important outcome using the GRADE approach (see Appendix F of the systematic review).

Data Synthesis and Analysis

Risk ratios (RRs) and 95% confidence intervals (CIs) for benefits and harms of treatment were analysed in Cochrane Collaboration's Review Manager and absolute effects were calculated as proportions per 1,000. In situations where there were no events in the control group, Review Manager automatically added 0.5 to each cell of the 2x2 table in order to allow for the calculation of RRs. Treatment at earlier versus later stages of fibrosis was also compared, where this data was available.

All data were processed with GRADEPro software and presented in table format (see Appendix G of the systematic review). Due to the small sample size of some studies, particularly for sub-group analyses, the optimal information size (OIS) for each outcome was calculated and used to inform the GRADE

assessments. Optimal information size is based on a two-sided α=0.05 and desired power of 0.8, which was determined using this calculator: http://www.stat.ubc.ca/~rollin/stats/ssize/b2.html .

The work group also established, a priori, clinical decision thresholds (CDT) for each patient important outcome, which dictated whether the clinical recommendation would be in favour or against treatment with direct-acting antiviral (DAA)-based regimens (OIS and CDT, Appendix I of the review).

Publication Bias

The small number of RCTs meant the reviewers could not assess for publication bias using funnel plots. Instead, they searched Clinicaltrials.gov for registered protocols of studies not conducted (or reported on).

Indirectness of the Evidence

In addition to issues of indirectness in the study population mentioned above, drawing conclusions about the effectiveness of DAA-based regimens for a treatment naïve population are limited by the fact that the reviewers did not include studies that compared individuals who received treatment to those that did not. Such trials (not to be confused with delayed treatment studies) were not identified in their review of the literature likely because since the mid-1990s and the availability of PR as an effective treatment, these trials have not been conducted. It would be unacceptable to conduct a trial where individuals identified with HCV in the control group would not receive any treatment for HCV.

Modelling Study

A modelling study was also commissioned by the task force and conducted by a team from the Toronto Health Economics and Technology Assessment Collaborative. This modelling study was used to examine the possible impact of screening under certain circumstances on hepatic mortality, hepatocellular carcinoma and decompensated cirrhosis. In the absence of empirical data, expert opinion was sought for four key model input parameters: 1) expected uptake of screening in the general population, 2) uptake of treatment in asymptomatic individuals, 3) genotype distribution, and 4) distribution of hepatic fibrosis scores in a primary care setting. Working group members identified five HCV experts, three of whom provided parameter estimates and ranges and the location of possible supplemental data supporting their estimates. Parameter estimates were established by calculating the mean value of the responses that the experts provided. The latest prevalence estimates from PHAC (2014) were used as inputs for the model for the general population and various subgroups.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The task force is an independent panel of clinicians and methodologists that makes recommendations about clinical interventions aimed at primary and secondary prevention. These recommendations were developed by a workgroup of seven members of the task force with scientific support from Public Health Agency of Canada (PHAC). The recommendations were informed by two independently conducted systematic reviews that addressed specific aspects of the guideline's analytic framework (Appendix 1 of the original guideline document [see the "Availability of Companion Documents" field]). The reviews excluded post-transplant patients, patients with human immunodeficiency virus (HIV), patients on hemodialysis and patients with occupational exposure; studies on all other population groups were sought, including higher-risk groups (e.g., with history of injection drug use) and higher-prevalence groups (e.g., birth cohort). A modelling study was also commissioned by the task force and conducted by a team from the Toronto Health Economics and Technology Assessment Collaborative. This modelling study was used to examine the possible impact of screening under certain circumstances on hepatic

mortality, hepatocellular carcinoma and decompensated cirrhosis.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to determine the quality of evidence and strength of recommendations (see the "Rating Scheme for the Strength of the Evidence" and "Rating Scheme for the Strength of the Recommendations" fields).

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations

Strong recommendations are those for which the Canadian Task Force on Preventive Healthcare (CTFPHC) is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention). A strong recommendation implies that most people will be best served by the recommended course of action and that the recommendation can be adopted in practice or as policy in most situations. Strong recommendations are normally based on high-quality evidence (i.e., high confidence in the estimate of the effect of an intervention). Strong recommendations may recommend in favour of an intervention (when there is high confidence of benefit) or against an intervention (when there is high confidence of harm). However, there are five circumstances in which the CTFPHC may consider a strong recommendation based on low- or very low-quality evidence:

- When low-quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high)
- When low-quality evidence suggests benefit and high-quality evidence suggests harm or a very high cost
- When low-quality evidence suggests equivalence of two alternatives, but high-quality evidence of less harm for one of the competing alternatives
- When high-quality evidence suggests equivalence of two alternatives and low-quality evidence suggests harm in one alternative
- When high-quality evidence suggests modest benefits and low-/very low-quality evidence suggests possibility of catastrophic harm

Weak recommendations are those for which the desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention), but appreciable uncertainty exists. Weak recommendations result when the balance between desirable and undesirable effects is small, the quality of evidence is lower, or there is more variability in the values and preferences of patients. In cases where the balance of cost and benefits is ambiguous, key stakeholders differ about the acceptability or feasibility of implementation, and the effects on health equity are unclear are likely to result in a weak recommendation. A weak recommendation implies that most people would want the recommended course of action, but that many would not. For clinicians, this means that they must recognize that different choices will be appropriate for each individual, and that they must help each person arrive at a management decision consistent with his/her values and preferences. Policy-making will require substantial debate and involvement of various stakeholders.

Cost Analysis

Cost-effectiveness

One cost-effectiveness analysis met the inclusion criteria for the screening review, and it focused on developing an economic model to project the lifetime health and economic effects of three "screen-and-treat" strategies compared with no screening, in a Canadian context. The screening scenario considered for all strategies was one-time antibody (Ab) screening offered during a visit to a primary care physician for an unrelated purpose; Ab-positive individuals were followed up with an HCV-ribonucleic acid (RNA)

test to confirm active infection. Individuals positive on both the Ab and RNA tests were assumed to be referred for treatment, as appropriate, according to Canadian guidelines. For individuals 25 to 64 years of age and living in Canada, screen-and-treat resulted in incremental cost-effectiveness ratios (ICERs) ranging from $34,783 per quality-adjusted life-year (QALY) to $42,398/QALY, when compared with no screening. For individuals 45 to 64 years of age, screen-and-treat resulted in ICERs ranging from $34,359/QALY to $44,034/QALY. One-way sensitivity analyses suggest the model was robust to screening acceptance rates and cost of screening.

Refer to the "Resource Use" and "Feasibility, Acceptability, Cost and Equity" sections in the original guideline document for additional information.

Method of Guideline Validation

Comparison with Guidelines from Other Groups

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The Feasibility, Acceptability, Cost, and Health Equity (FACE) tool was used with organizational stakeholders to gain their perspective on the priority, feasibility, acceptability, cost and equity of the recommendation. The FACE survey was pilot-tested with this guideline as part of a validation exercise. Stakeholder organizations that provided input on the recommendation using the FACE survey are listed in Appendix 3 of the original guideline document (see the "Availability of Companion Documents" field).

The recommendations were revised and approved by the entire task force and underwent external review by academic and clinical experts.

Other Guidelines

Population-based screening for hepatitis C virus (HCV) is not recommended by the task force. The task force recommendation aligns with recently published clinical guidelines from the World Health Organization; National Institute for Health and Care Excellence; Scottish Intercollegiate Guidelines Network; Immigration, Refugees and Citizenship Canada; UK National Screening Committee; and the Gastroenterological Society of Australia. It partly aligns with guidelines from the Canadian Collaboration for Immigrant and Refugee Health, the U.S. Preventive Services Task Force (USPSTF) and the U.S. Centers for Disease Control and Prevention (CDC) (1998) (see Table 1 in the original guideline document). Although there is variation in definitions, most jurisdictions recommend some sort of risk-based testing.

The more recent guideline from CDC (2012) and the USPSTF guideline recommend one-time screening for those born between 1945 and 1965. This recommendation relies on indirect evidence such as prevalence (estimated to be 3.25% in the US, which is four times higher than in Canada at 0.8%), attainment of sustained virologic response (a surrogate outcome) and the ability of practitioners to influence screening uptake. The CDC and USPSTF recommendations acknowledge the lack of direct evidence on effectiveness of screening in this cohort and the potential for screening to increase overall harms in this population related to overdiagnosis and overtreatment.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major

Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The hepatitis virus C (HCV) prevalence in most adults in the general Canadian population is low and direct evidence examining the benefits and harms of screening for HCV is not available. Thus, the task force recommends against screening adults who are not at elevated risk for HCV. Not screening for HCV will focus the limited health care resources to test (and treat) individuals at elevated risk for HCV and to provide other medical interventions that are proven to be of benefit.

Potential Harms

- The task force recommendation places a relatively higher value on 1) the anticipated increase in harm resulting from diagnosing and treating individuals who screen positive but would have never developed hepatitis C virus (HCV)-related disease during their lifetime; 2) false positives and false negatives, which could lead to unnecessary anxiety and/or false reassurance; 3) the potential for screening to increase inequity, given that among those who do not meet current eligibility criteria (e.g., specific comorbidities), only wealthier individuals or those with private insurance would obtain earlier access to treatment not currently funded by government; 4) the unknown magnitude of benefit of treatment on reducing risk of transmission; and 5) the very large impact that screening and treatment would have on health care budgets, and associated opportunity costs (i.e., the limit this would place on the ability to provide other health care interventions that would have to be forgone for lack of funds, despite being supported by better evidence.
- Only one uncontrolled retrospective study was found that reported on harms of screening. That study was a retrospective review of records from a large urban U.S. Department of Veterans Affairs hospital; the study reported that of 12,485 people screened for HCV in 2001, only one patient experienced serious harm (hospitalization for pain control following liver biopsy).

Qualifying Statements

Qualifying Statements

- The views of the funding body have not influenced the content of the guideline; competing interests have been recorded and addressed. The views expressed in this article are those of the Task Force and do not necessarily represent those of the Public Health Agency of Canada.
- The evidence from the treatment review has several key limitations that reduce its applicability to this guideline. 1) Study participants were not identified by screening and could differ from people detected by population-based screening. It is uncertain whether the effects of treatment would be similar for symptomatic and screened, asymptomatic patients. 2) The identified studies did not include a comparison to an untreated control group. 3) Evidence of benefit associated with newer treatments was restricted to surrogate outcomes assessed following a relatively short interval, given the chronic nature of hepatitis C virus (HCV) infection, and did not consider the potential risk of occurrence of hepatocellular carcinoma after achieving sustained virologic response.
- The modelling study commissioned by the task force has several important limitations that contribute to the uncertainty in the estimate of the effect: 1) an inability to consider potential differences in long-term outcomes between initiating treatment at earlier versus later stages of liver fibrosis, 2) the possibility that the baseline risk of disease progression used for the model (based on

nonscreened populations) is higher than that for the asymptomatic screened population, which would translate into an overestimation of the benefit of screening, 3) an inability to take into consideration the harms of overdiagnosis and overtreatment that result from screening, and 4) the inherent inability of modelling to account for unknown factors that may influence screening outcomes.

Gaps in Knowledge

An important gap is the lack of studies that examine the benefits, harms and other potential consequences of screening asymptomatic populations. Randomised controlled trials (RCTs) that compare treatment at earlier versus later stages of liver fibrosis are needed. A large population-based prevalence study of chronic HCV in Canada is also lacking. Small studies, primarily in lower- or higher-risk groups and using modelled data, are available, but the confidence in the certainty of those estimates is low. Although there is some evidence on the natural history of HCV infection, there is uncertainty about the factors that influence the progression of liver disease and how these factors may affect the proportion of people who go on to develop end-stage liver disease, in some cases, despite achieving sustained virologic response. Although there are observational data examining the association of sustained virologic response with long-term outcomes important to patients, additional studies are needed to ascertain whether sustained virologic response associated with newer agents (direct-acting antivirals [DAAs]) yields similar outcomes.

Implementation of the Guideline

Description of Implementation Strategy

Considerations for Implementation

The task force recommendation applies to individuals who are not pregnant or at elevated risk for hepatitis C virus (HCV). Subgroups of the population who are at increased risk for HCV (and not included in this recommendation) may require special attention from clinicians. A joint 2009 recommendation from College of Family Physicians of Canada (CFPC) and Public Health Agency of Canada (PHAC), although not based on a systematic review of the evidence, addressed those individuals who are at increased risk. That guidance suggests testing for HCV in "anyone with risk behaviours for HCV, with potential exposure to HCV, and/or with clinical clues suspicious for HCV." Populations targeted in the CFPC/PHAC guideline include people who inject drugs (currently or in the past); individuals who have been incarcerated; individuals who may have been exposed to contaminated blood, blood products or medical equipment; and those who have travelled or resided in endemic regions.

Some immigrants are at increased risk for HCV because they are from countries where HCV infection is common. Unlike the nonimmigrant population, these persons are at increased risk for HCV because of iatrogenic exposure in their country of origin (e.g., lack of standard precautions, or as a result of medical or dental procedures with contaminated equipment) and not necessarily from injection drug use or other higher-risk behaviours. The CFPC/PHAC guidance recommends testing for HCV in individuals who were "born, traveled or resided in a region in which HCV infection is more common." A list of endemic countries and a related map are provided in Appendix 6 of the original guideline document (see the "Availability of Companion Documents" field).

More persons in subgroups such as the Indigenous population (3% prevalence) and the cohort born from 1950 to 1975 (0.8% prevalence) are diagnosed with chronic HCV; these populations have a higher proportion of individuals at higher risk for HCV because of identifiable risk factors. For example, removing from the Indigenous population people who inject drugs would reduce the HCV prevalence from 3% to 0.5%. Individuals from the Indigenous population who are not otherwise at increased risk are, therefore, included in the present task force guidance, which recommends against screening adults who are not at elevated risk. Similarly, the increased reported prevalence in the cohort born between 1950 and 1975 is likely driven by an increased prevalence of risk behaviours or potential exposures, rather than birth year

per se. In the judgment of the task force, neither Indigenous people nor members of the 1950–1975 birth cohort should be screened for HCV in the absence of other characteristics that would place them at increased risk for HCV.

The task force considered the possibility of screening a birth cohort; that is, one-time testing of all people born, for example, between 1950 and 1975. Most individuals in the birth cohort who are at elevated risk are included in the joint CFPC/PHAC guideline. Following this risk-based guideline will likely increase the identification of those who will benefit most from testing. Those born from 1950 to 1975, who are not otherwise at increased risk, are included in the present task force guidance, which recommends against screening adults who are not at elevated risk. More evidence would be needed before making a recommendation about birth cohort testing, separate from adults in the general population.

The task force developed knowledge translation tools to help clinicians assess their patients' risk for HCV, so that testing can be offered to those at increased risk. These are available at http://canadiantaskforce.ca/tools-resources/hepatitis-c-2/ .

Monitoring and Evaluation

Given that the task force has recommended against screening adults who are not at elevated risk of HCV, a clear indicator of the uptake of this guideline would be decreased screening of individuals who do not present with risk factors.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Quick Reference Guides/Physician Guides

Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Canadian Task Force on Preventive Health Care. Recommendations on hepatitis C screening for adults. CMAJ. 2017 Apr 24;189(16):E594-E604. [100 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

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Guideline Committee

Canadian Task Force on Preventive Health Care (CTFPHC)

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Financial Disclosures/Conflicts of Interest

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The views of the funding bodies have not influenced the content of the guideline; competing interests have been recorded and addressed.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Canadian Medical Association Journal (CMAJ) Web site.

Availability of Companion Documents

The following are available:

- Canadian Task Force on Preventive Health Care. Recommendations on hepatitis C screening for adults. Online appendices 1-6. CMAJ. 2017 Apr 24;189(16):E594-E604. Available from the Canadian Medical Association Journal (CMAJ) Web site.
- Screening for hepatitis C: a systematic review. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Mar. 206 p. Available from the Canadian Agency for Drugs and Technologies in Health (CADTH) Web site.
- Reyes Domingo F, Holmes NM, Jaramillo Garcia A, et al. Treatment for hepatitis C virus: a systematic review and meta-analysis. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2017 Apr. 249 p. Available from the Canadian Task Force on Preventive Health Care (CTFPHC) Web site.
- Reyes Domingo F, Jaramillo Garcia A, Chawla M, Morissette K, Holmes, N. Treatment review protocol: systematic review and meta-analysis of hepatitis C treatments for non-pregnant, treatment-naïve adults. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2015 Nov 25. 20 p. Available from the CTFPHC Web site.
- Screening for hepatitis C virus: a systematic review and meta-analysis – project protocol. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2015 Dec. 53 p. Available from the CADTH Web site.
- Recommendations on hepatitis C screening for adults. Clinician FAQ. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2017 Apr. 2 p. Available in English and French from the CTFPHC Web site.
- Screening for hepatitis C. Clinician summary. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2017 Apr. 3 p. Available from the CTFPHC Web site.
- Wong W, Erman A, Krahn M. Model-based projection of health and economic effect of screening hepatitis C in Canada. 2016 update. Final report. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2016 Nov 22. 74 p. Available from the CTFPHC Web site.
- Patient preferences in considering hepatitis C screening and treatment outcomes: phase two. Prepared for the Canadian Task Force on Preventive Health Care. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2016 Aug 8. 52 p. Available from the CTFPHC Web site.
- Hepatitis C screening in adults: clinical practice guideline. CMAJ podcast. Available from the CTFPHC Web site.
- Canadian Task Force on Preventive Health Care procedure manual. Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2014 Mar. 83 p. Available from the CTFPHC Web site.
- Putting prevention into practice: GRADE (Grades of recommendation, assessment, development, and evaluation). Ottawa (ON): Canadian Task Force on Preventive Health Care (CTFPHC); 2011. 2 p. Available in English and French from the CTFPHC Web site.

A continuing professional development (CPD) activity related to this guideline is available on the CMAJ Web site.

There is a CTFPHC mobile app for primary care practitioners available for download from the CTFPHC Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on May 18, 2017. The information was not verified by the guideline developer.

This NEATS assessment was completed by ECRI Institute on June 22, 2017. The guideline developer did not acknowledge or provide confirmation for this NEATS assessment.

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